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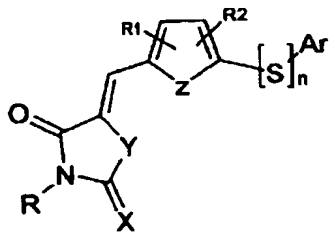
(58) Field of Search
Other: CAS ONLINE

(54) Abstract Title
[(Aryl-/arylthio-)aryl]methylene substituted azole & azine derivatives and their therapeutic use as antibacterials

(57) Compounds of Formula 1



Formula 1

Where: X is O, CHCN or S; Y is O, NH, CH_2, S or NHCO; Z is O, S, NH, or CH=CH; n=0 or 1; Ar is an optionally substituted single or fused carbocyclic or heterocyclic aromatic ring, (where, for example, the aromatic ring may have up to three substituents independently selected from C_{1-6} alkyl, halogen, hydroxy, C_{1-6} alkoxy, NO_2, CF_3, CN, COOH, COOR3, CONR4R5);

R, R3, R4 and R5 are independently selected from the group consisting of H, or a substituent as claimed or as otherwise described (eg an optionally substituted alkyl, phenyl or heterocycle); R1 and R2 are independently selected from the group consisting of hydrogen, halogen, OH, COOH, CN, substituted or unsubstituted C_{1-6} alkyl inhibit the chorismate synthase enzyme in the shikimate pathway and may be used as antibacterial agents, eg to treat infections caused by gram positive organisms such as S.aureus.

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AZOLE COMPOUNDS AND THEIR THERAPEUTIC USE

Field of the Invention

This invention relates to chorismate synthase inhibitory rhodanine analogues, as well as compositions containing the same and to their therapeutic use, particularly those used for treating or preventing infections and diseases associated therewith.

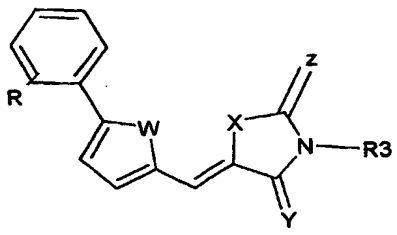
Background to the Invention

Several chemical classes of compound are known that possess considerable antibacterial activity, and these have proven of immense value in the treatment of bacterial diseases and infection. They include among others, the penicillins, the cephalosporins, the aminoglycoside antibiotics, vancomycin analogues and the sulfonamide drugs.

The mechanism of action of a number of known antibiotics is by the direct inhibition of enzymes of essential bacterial biosynthetic pathways. These include, amongst others, trimethoprim and the sulfonamide drugs.

Chorismate synthase, an enzyme in the shikimate pathway has been shown to be essential for bacterial viability (EP0913480). Compounds that inhibit this enzyme could therefore be useful antibacterial agents.

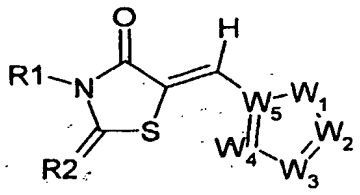
Compounds of similar structure to those of the invention have been described previously, but have not been described as chorismate synthase inhibitors nor reported to have antibacterial activity. For example, Patent WO2000010573 claims the general structure shown in Figure 1 as antiviral agents, in which R3 is not hydrogen.



X=S, O or NRa (Ra=H, C1-5 alkyl)
Y=O or S; Z=O,S or NRh (Rh=H, alkyl)
Two rings chosen from (un)substituted phenyl; alkylphenyl; (un)substituted heterocycles (furan, thiophene, oxazole, oxadiazole, pyridine, pyrimidine, pyrazole, triazole, pyridazine, 1,3-oxathiolane, thiazole, thiadiazole, imidazole, tetrazole, pyrrole, triazine
R3 C1-10 aliphatic acid, preferred acetic acid, propionic acid, or benzoic acid, or alkylphenyl (substituted or unsubstituted)

Figure 1

Patent WO2000032598 claims the general structure shown in Figure 2 as TNF receptor agonists for the treatment of inflammatory disease.



W1-W5 together - aliphatic
heterocyclic
heteroaromatic

R2 - O, S

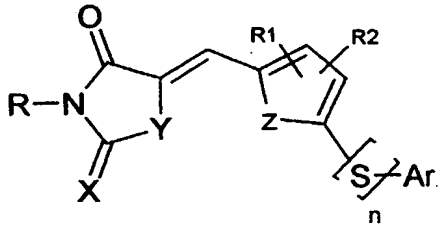
R1 - H, heteroaromatic, (cyclo)alkyl

Figure 2

The compounds described in the invention are novel, and without wishing to be bound by theory, possess a method of action distinct from previously described antibiotics.

Summary of the Invention

This invention relates to compounds, and more specifically to azole analogues and to their pharmaceutical compositions defined by Formula 1, or a pharmaceutical acceptable salt thereof.



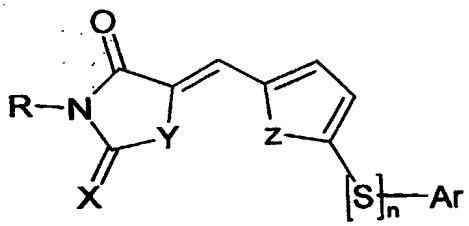
Formula 1

Where: X is O, CHCN or S; Y is O, NH, CH_2, S or NHCO; Z is O, S, NH, or CH=CH; n=0 or 1
Ar is an optionally substituted single or fused carbocyclic or heterocyclic aromatic ring. These include but are not limited to phenyl, napthyl, pyridine, quinoline, pyrimidine, imidazole, furan, thiadiazole derivatives. The bond to the Ar group can be to any of its ring atoms. The aromatic ring may have up to three substituents independently selected from C_{1-6} alkyl, halogen, hydroxy, C_{1-6} alkoxy, NO_2, CF_3, CN, COOH, COOR3, CONR4R5.
R, R3, R4 and R5 are independently selected from a group consisting of H, substituted or unsubstituted C_{1-6} alkyl, CH_2COOH, substituted or unsubstituted phenyl or heterocycles; R1, R2 are independently selected from the group consisting of hydrogen, halogen, OH, COOH, CN, substituted or unsubstituted C_{1-6} alkyl.

Particularly preferred compounds are those where:
n is 0 or 1; X is S or CHCN; Y is S; Z is O or S; R is H; and Ar is as defined above.

Particularly preferred compounds are illustrated in Table 1.

Table 1



No	R	X	Y	Z	n	Ar
1	H	S	S	O	0	3-CF_3Ph
2	H	S	S	S	0	3-BrPh
3	CH_2 (2-furyl)	S	S	O	0	3-CF_3Ph
4	H	S	S	O	0	4-Cl-3-NO_2Ph
5	H	S	S	S	0	3-CF_3Ph
6	H	S	S	O	0	2-Cl-3-CF_3Ph
7	H	S	S	O	0	3-OCF_3Ph
8	H	S	S	O	0	4-CF_3Ph
9	H	S	S	O	0	3-COOH-4-OHPh
10	4-CF_3Bn	S	S	O	0	3-COOHPh
11	3-ClPh	S	NH	S	0	3-COOHPh
12	H	S	S	O	0	2,6-diClPh
13	H	S	S	O	0	3-COOMePh
14	H	S	S	O	1	3-CF_3Ph
15	H	S	S	O	1	4-NO_2Ph
16	H	S	S	O	1	2-MePh
17	H	S	S	O	1	4-py
18	H	S	S	O	1	6-(3-COOH)Py
19	H	S	S	O	1	2-(3-COOH)Py
20	H	S	O	O	1	2-(3-COOH)Py
21	H	O	S	O	1	2-(3-COOH)Py
22	H	S	S	O	1	2-OHPh
23	H	S	S	O	1	2-OMePh
24	H	S	O	O	1	6-(3-COOH)Py
25	H	S	O	O	1	6-(3-$CONHCH_2CH_2COOH$)Py
26	CH_2COOH	S	S	O	1	6-(3-COOH)Py
27	H	S	S	O	1	2-pyrimidine
28	H	CHCN	S	O	0	3-CF_3Ph

Compounds of the invention have therapeutic utility as antibacterial agents. They are especially useful for the treatment of infections caused by gram positive organisms such as *S. aureus*. In particular, they exhibit inhibition of the enzyme chorismate synthase in shikimate pathway which has been shown to be essential for bacterial viability (EP0913480). The compounds and their pharmaceutically acceptable salts are claimed as the active ingredients in medicines for the treatment of bacterial infection in man and animals.

Description of the Invention

Certain compounds of this invention are preferred

The term "C_{1-6} alkyl" as used herein refers to straight and branched chain alkyl groups having up to 6 C atoms. Examples are methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl and tert-butyl. "Alkyl" may have the same meaning. "Halogen" means F, Cl, Br or I. "Alkoxy" means C_{1-6} alkyl-O-. "Heterocyclyl" means

a saturated, unsaturated or aromatic ring of 5 to 8 atoms containing one or more heteroatoms such as O, S or N, and which may be bonded *via* any C or ring atom.

Compounds of formula 1 may contain one or more chiral centres and exist in optically active forms. When a compound of formula 1 or a salt thereof contains a single chiral centre (for example sec-butyl) it may exist in two enantiomeric forms. The present invention includes individual enantiomers and mixtures of these enantiomers. The enantiomers may be obtained by methods known to those skilled in the art. Such methods typically include resolution via formation of diastereomeric salts or complexes which may be separated, for example, by crystallisation; resolution via formation of diastereomeric derivatives or complexes which may be separated, for example, by crystallisation, gas-liquid or liquid chromatography; selective reaction with one enantiomer by reaction with an enantiomer-specific reagent, for example, enzymatic esterification, oxidation or reduction, followed by separation of the modified and unmodified enantiomers; or gas-liquid or liquid chromatography on a chiral support such as silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation processes described above, at least one further step will subsequently be required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into another by asymmetric transformation.

When a compound of formula 1 or a salt thereof contains more than one chiral centre it may exist in diastereomeric forms. The diastereomeric pairs may be separated by methods known to those skilled in the art, for example, chromatography or crystallisation and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereomer of compounds of formula 1 and mixtures thereof.

Some compounds of formula 1 may exist in the form of solvates, for example, hydrates, which also fall within the scope of the present invention.

The compounds of formula 1 may form organic or inorganic salts, for example, the compounds of formula 1 may form addition salts with inorganic or organic acids, e.g. hydrochloric acid, hydrobromic acid, fumaric acid, tartaric acid, citric acid, sulfuric acid, hydiodic acid, maleic acid acetic acid, succinic acid, benzoic acid, pamoic acid, palmitic acid, dodecanoic acid and acidic amino-acids such as glutamic acid. Such compounds of formula 1 may form base addition salts, for example, with alkali metal hydroxides e.g. sodium hydroxide, with amino-acids e.g. lysine or arginine or with organic bases e.g. meglumaine. It will be appreciated that such salts, provided that they are pharmaceutically acceptable may be used in therapy in place of compounds of formula 1. Such salts are prepared by reacting the compound of formula 1 with a suitable acid or base in a conventional manner. Such salts may also exist in the form of solvates, for example, hydrates. The present invention includes each salt and any solvate thereof.

Certain compounds of formula 1 or salts thereof may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

"Pharmaceutically acceptable salts" are acid addition salts which can be prepared by any of the art recognised means. Typical acid addition salts include hydrochloride, hydrobromide, hydroiodide, sulphate, phosphate, acetate, propionate, lactate, malate, succinate, tartrate, cyclohexanesulphamates,

As used hereinafter, the term "active compound" denotes a compound of formula 1 including pharmaceutically acceptable salts thereof. In therapeutic use, the active compound may be administered orally, rectally, parenterally, topically, ocularly, aurally, nasally, intravaginally or to the buccal cavity, to give a local and/or systemic effect. Thus the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions.

Tablets may be prepared from a mixture of the active compound with fillers such as lactose or calcium phosphate, disintegrating agents, for example maize starch, lubricating agents, for example magnesium stearate, binders for example microcrystalline cellulose or polyvinyl pyrrolidone and other optional ingredients known in the art to permit tableting the mixture by known methods. The tablets may, if desired, be coated using known methods and excipients which may include enteric coating using for example hydroxypropylmethylcellulose phthalate. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate.

Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by known methods and if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 0.1 to 1000 mg (for example 10 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, or 800 mg) of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethylcellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example sunflower oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

Compositions for topical administration are also preferred compositions of the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as petrolatum and/or light liquid paraffin, dispersed in an aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil, petrolatum and/or a wax e.g. paraffin wax or beeswax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent e.g. basified Carbomer BP, in the presence of water. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, such as described above, together with a potential transdermal accelerate such as dimethyl sulphoxide or propylene glycol.

Compositions of the invention suitable for rectal administration are known pharmaceutical forms for such administration, for example suppositories with hard fat, synthetic glycerides or polyethylene glycol bases.

Compositions of the invention suitable for parenteral administration are known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

Compositions of the invention suitable for inhalation via the mouth and/or the nose are the known pharmaceutical forms for such administration, for example aerosols, nebulised solutions or powders. Metered dose systems, known to those skilled in the art, may be used.

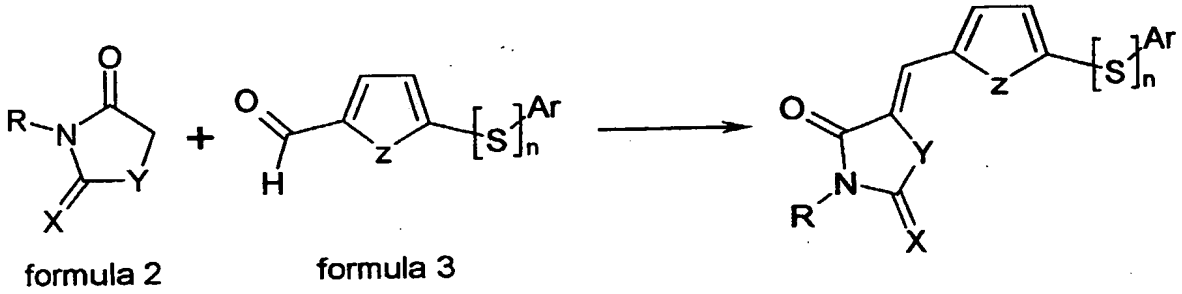
Compositions suitable for application to the buccal cavity include slow dissolving tablets, troches, chewing gum, gels, pastes, powders, mouthwashes or rinses.

The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion, or from a source of the compound placed within the body, internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may be a) liquid such as an oily solution or suspension of the compound to be infused for example in the form of a very sparingly water-soluble

derivative such as a dodecanoate salt or b) solid in the form of an implanted support for example of a synthetic resin of waxy material for the compound to be infused. The support may be a single body containing the entire compound or a series of several bodies each containing part of the compound to be delivered.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

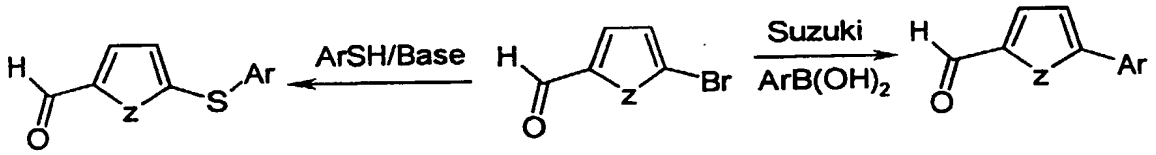
The componds of formula 1 described above can be prepared by the route shown in Scheme 1. The general method of preparation of these compounds is the aldol condensation of azole analogues of the formula 2 with an aldehyde of formula 3, wherein X, Y, Z and R, n, Ar are as defined previously. This condensation can be carried out in alcoholic solvents in the presence of a base such as ammonia, ammonium salts, or piperidine, or with a mineral acid catalyst at a temperature range between -80° to 250°C. A particularly favored procedure is the use of anhydrous sodium acetate in glacial acetic acid, with heating at reflux for 1-24 hours. References to this procedure include: G.R.Newkome and A.Naykak in Advances in Heterocyclic Chemistry, A.R.Katritzky and A.J.Boulton, eds., Academic press, New York, NY, Vol 25, Pg83.



formula 2 formula 3

Scheme 1

The aldehyde can be prepared by Suzuki reaction or by direct nucleophilic substitution on furan or thiophene ring (Scheme 2).



formula 4

Scheme 2

The reactions described herein will be generally understood by one of ordinary skill in the art. The starting materials are available or can readily be prepared by one of ordinary skill in the art.

General Procedure for the Preparation of the Examples.

a. Coupling of aldehydes and azole analogues

To a solution of the azole analogue of formula 2 (1.0 mmol) in acetic acid (5 ml) was added NaOAc (3.0 mmol), followed by a solution of the aldehyde of formula 3 (1.0 mmol) in acetic acid (2 mL). The solution was heated for 10-240 minutes, then cooled. The residue was triturated with diethyl ether, the solid collected, washed with ethanol, then with water and dried overnight in a desiccator over P_2O_5 to give the target compound of formula 1. Compounds were analysed by LCMS and ^{1}HNMR.

b. Aldehydes of formula 3 prepared by Suzuki reactions

The mixture of an aryl bromide of formula 4 (1.0 mmol), an arylboronic acid (1.05 mmol) in 5 mL 1-propanol was stirred at room temperature under nitrogen for 20 minutes, allowing solids to dissolve. The resulting solution was treated with palladium acetate (0.003 mmol), triphenylphosphine (0.009 mmol), 2M sodium carbonate (1.2 mmol), and deionized water (1mL), and heated to reflux under a nitrogen atmosphere for 2-24 hours (reaction monitored by LC/MS). Water (10 mL) was added to the reaction mixture, and stirred open to the atmosphere for 1 hour while cooling to room temperature. The darkened mixture is extracted with ethyl acetate. Combined extracts were washed with 5% sodium bicarbonate, followed by brine, dried over $MgSO_4$, then filtered through celite. The filtrate was concentrated under the reduced pressure to give a yellow solid which was further purified by crystallization from hexane-ethyl acetate. Compounds were analysed by LCMS and ^{1}HNMR.

c. Aldehydes of formula 3 prepared by direct nucleophilic substitution

The mixture of an aromatic thiol (1.0 mmol) and sodium hydride (1.0 mmol) in DMF (5 mL) was stirred at room temperature under nitrogen for 15 minutes, then an aryl bromide of formula 4 was added. The resulting mixture was stirred at room temperature for 1- 12 hours (LC/MS monitoring the reaction). The reaction mixture was poured into water (if necessary, neutralised to pH7), and extracted with ethyl acetate. The organic extracts were combined, dried, and concentrated. The crude product was purified by recrystallization in a suitable solvent or by flash column chromatography.

Analytical data for compounds from the invention are given in Table 2.

Table 2

Bacterial chorismate IC_{50} data for compounds of the invention

Example No.	$IC_{50}(\mu M)$ SpCS	SaCS
1	4.2	
2	11	
3	2.3	1.5
4	2.6	0.46
5	5.5	13.5
6	2.1	3.2
7	8.3	22.1
8	11.8	
9	21	
10	1.5	
11	4.5	
12	4.3	
13	5.2	
14	20	
15	11.5	
16	12.4	
17	8.0	6.0
18	0.56	1.2
19	2.8	2.7
20	9.8	1.6

21	0.6	2.6
22	5.5	
23	10.5	
24	2.0	
25	7.4	
26	7.3	
27	3.2	
28	2.0	4.5

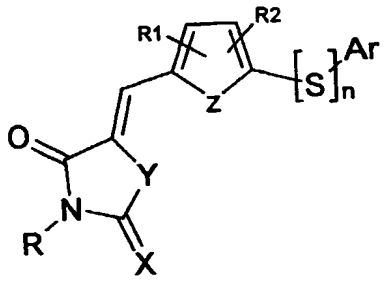
SpCS = *Streptococcus pneumoniae* chorismate synthase, SaCS = *Staphlococcus aureus* chorismate synthase.

Measurement of IC_{50}

The inhibitory effect of a compound can be described by an IC_{50} value, that is the concentration of inhibitor at which half (50%) inhibition of the maximal (100%) inhibition occurs. IC_{50} values were determined by measuring the extent of inhibition over a range of concentrations of the compound, preferably a range where the degree of inhibition varied from no inhibition (0%) to complete inhibition (100%). The IC_{50} value can be estimated from a plot of % inhibition against concentration of inhibitor, or can be calculated using data fitting programs, such Grafit (Elsevier) or EnzFitter (Biosoft).

Claims

1. A compound, for therapeutic use, of Formula 1



Formula 1

Where: X is O, CHCN or S; Y is O, NH, CH_2, S or NHCO; Z is O, S, NH, or CH=CH; n=0 or 1 Ar is an optionally substituted single or fused carbocyclic or heterocyclic aromatic ring. These include but are not limited to phenyl, napthyl, pyridine, quinoline, pyrimidine, imidazole, furan, thiadiazole derivatives. The aromatic ring may have up to three substituents independently selected from C_{1-6} alkyl, halogen, hydroxy, C_{1-6} alkoxy, NO_2, CF_3, CN, COOH, COOR3, CONR4R5.

R, R3, R4 and R5 are independently selected from the group consisting of H, C_{1-6} alkyl optionally substituted with one or more halogen, hydroxy, amino, carboxy, carboxamide groups, optionally substituted phenyl or heterocycles; R1 and R2 are independently selected from the group consisting of hydrogen, halogen, OH, COOH, CN, substituted or unsubstituted C_{1-6} alkyl.

2. A compound of claim 1 where

n is 0 or 1, X is S or CHCN, Y is S, Z is O or S, R is H, Ar is substituted and unsubstituted phenyl (optionally substituted by C_{1-6} alkyl, halogen, OH, C_{1-6} alkoxy, NO_2, CF_3, CN, COOH, COOR3, CONHR4), pyridine (optionally substituted by C_{1-6} alkyl, halogen, OH, C_{1-6} alkoxy, NO_2, CF_3, CN, COOH, COOR3, CONHR4), pyrimidine, thiadizole.

3. A compound of claim 1, selected from:

(5Z)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one

(5Z)-5-{[5-(3-bromophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

(5Z)-3-(2-furylmethyl)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one

(5Z)-5-{[5-(4-chloro-3-nitrophenyl)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

(5Z)-2-thioxo-5-({5-[3-(trifluoromethyl)phenyl]thien-2-yl}methylene)-1,3-thiazolidin-4-one

(5Z)-5-({5-[2-chloro-5-(trifluoromethyl)phenyl]-2-furyl}methylene)-2-thioxo-1,3-thiazolidin-4-one

(5Z)-2-thioxo-5-({5-[3-(trifluoromethoxy)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one

(5Z)-2-thioxo-5-({5-[4-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-4-one

2-hydroxy-5-{5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoic acid

3-[5-((Z)-{4-oxo-2-thioxo-3-[4-(trifluoromethyl)benzyl]-1,3-thiazolidin-5-ylidene}methyl)-2-furyl]benzoic acid

3-(5-{(Z)-[1-(3-chlorophenyl)-5-oxo-2-thioxoimidazolidin-4-ylidene]methyl}thien-2-yl)benzoic acid

(5Z)-5-{[5-(2,6-dichlorophenyl)thien-2-yl]methylene}-2-thioxo-1,3-thiazolidin-4-one

methyl 3-{5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}benzoate

(2E/Z)-[(5Z)-4-oxo-5-({5-[3-(trifluoromethyl)phenyl]-2-furyl}methylene)-1,3-thiazolidin-2-ylidene]acetonitrile

5. A compound of claim 1, selected from:

(5Z)-2-thioxo-5-[(5-{[3-(trifluoromethyl)phenyl]thio}-2-furyl)methylene]-1,3-thiazolidin-4-one

(5Z)-5-({5-[(4-nitrophenyl)thio]-2-furyl}methylene)-2-thioxo-1,3-thiazolidin-4-one

(5Z)-5-({5-[(2-methylphenyl)thio]-2-furyl}methylene)-2-thioxo-1,3-thiazolidin-4-one

(5Z)-5-{[5-(pyridin-4-ylthio)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

6-({5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

2-({5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

2-({5-[(Z)-(4-oxo-2-thioxo-1,3-oxazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

2-({5-[(Z)-(2,4-dioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

(5Z)-5-({5-[(2-hydroxyphenyl)thio]-2-furyl}methylene)-2-thioxo-1,3-thiazolidin-4-one

(5Z)-5-({5-[(2-methoxyphenyl)thio]-2-furyl}methylene)-2-thioxo-1,3-thiazolidin-4-one

6-({5-[(Z)-(4-oxo-2-thioxo-1,3-oxazolidin-5-ylidene)methyl]-2-furyl}thio)nicotinic acid

3-({[6-({5-[(Z)-(4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene)methyl]-2-furyl}thio)pyridin-3-yl]carbonyl}amino)propanoic acid trifluoroacetate

2-[(5-{(Z)-[3-(carboxymethyl)-4-oxo-2-thioxo-1,3-thiazolidin-5-ylidene]methyl}-2-furyl)thio]nicotinic acid

(5Z)-5-{[5-(pyrimidin-2-ylthio)-2-furyl]methylene}-2-thioxo-1,3-thiazolidin-4-one

6. A pharmaceutical composition comprising as an active ingredient a compound of any preceding claim, together with a carrier or diluent.

7. Use of a compound of any of claims 1 to 5, for the manufacture of a medicament for the treatment of a bacterial infection.

8. The use of claim 7, wherein the infection is caused by a gram positive organism.

9. The use of claim 8, wherein the organism is *S. aureus*.

Application No: GB 0207411.0
Claims searched: 1-9

Examiner: Stephen Quick
Date of search: 26 June 2003

Patents Act 1977 : Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1-9	Farmaco, 1999, Vol. 54(7), pages 475-478, see especially tables 1 & 2 and sections 4, 4.1 & 5 (page 477-478)
X	1-6	WO 01/93841 A2 (PROLIFIX), see pages 1 (lines 12-17), 11 (line 7ff) & 74 (lines 3-10), and (for example) compounds 20, 70 & 78 on pages 33, 42 & 44 respectively
X	1-6	WO 01/77091 A2 (TULARIK), see page 2 (lines 22-25), page 29 (lines 10-13), example 9 (pages 36-38) and compounds 111-117 (figures 2P & 2Q)
X	1-6	WO 00/32598 A1 (STRUCTURAL BIOINFORMATICS), see page 5 (line 2ff), page 27 line 26 to page 28 last line and (for example) examples 5, 8, 10 & 12; acknowledged in this application
X	1-6	WO 00/10573 A1 (VIROPHARMA), see page 3 (line 16ff), page 7 (lines 7-10), page 43 line 21 to page 44 line 1 and (for example) page 44 lines 24-25, and (for example) examples 1-7 (page 26ff); acknowledged in this application
X	1-6	Proceedings of the National Academy of Sciences of the United States of America, 2001, Vol. 98(21), pages 11879-11884, see especially page 11879 (abstract, first four sentences; and two sentences immediately preceding title "materials and methods") and page 11880 (table 1, entries 1, 2, 4 & 8-10; and compound 5B981 in figure 1 & table 2)
X,E	6	WO 02/062337 A1 (SMITHKLINE BEECHAM) 15.08.2002, see examples 11, 34 & 35
X,E	6	WO 02/051409 A1 (GERON; KYOWA HAKKO KOGYO) 04.07.2002, see page 12 lines 8-11 and (for example) example 1

Application No: GB 0207411.0
Claims searched: 1-9

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Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC[V]:

Worldwide search of patent documents classified in the following areas of the IPC[7]:

The following online and other databases have been used in the preparation of this search report:

CAS ONLINE

BNSDOCID: <GB_____2387172A__I_>